An artificial niche preserves the quiescence of muscle stem cells and enhances their therapeutic efficacy.

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Public Summary:
Muscle tissue is homing a population of adult muscle stem cells (MuSCs), which has a remarkable capacity to regenerate the original tissue following an injury. Typically, these MuSCs reside in a dormant state, called quiescence. Only when stimulated they wake up, activating and starting to proliferate to eventually repair the tissue. However, when isolated from their native “home”, called the niche, these cells lose their regenerative potential, such as when cultured in a petri dish. This loss of potency represents a limitation for cell therapies. Indeed, when trying to isolate the MuSCs from a patient to correct them, like in the case of genetic mutations that result in muscular dystrophies, then reintroducing the corrected MuSCs in the body, they cannot regenerate the tissue efficiently anymore. To overcome this problem, we decided to reproduce this niche in a petri dish. To this end, we assembled natural protein that normally constitute the natural niche, fabricating engineered muscle fibers (EMFs) that look and behave like natural ones. We also measured and reproduced the right degree of elasticity of the muscle fiber to create on these EMFs a “bed” for MuSCs that allows these cells to remain quiescent. Moreover, to support this quiescent state, we generated a special broth to culture MuSCs on EMFs. To understand which molecules were required to maintain this quiescence, we analyzed quiescent MuSCs individually, by determining which genes were active or inactive, and then comparing them with single activated MuSCs. We then created an artificial intelligence (AI), based on machine learning software. This AI helped us in recognizing the best receipt, among all conditions tested, capable of maintaining isolated MuSCs in their quiescent state in EMFs. When these MuSCs, genetically modified to emit bioluminescent light, were eventually transplanted into muscles of recipient immunocompromised mice, we observed non-invasively the light emitted. Artificial niches were capable to preserve the potency of these MuSCs, compared to MuSCs cultured in a petri dish, indicating their higher potency. Finally, we replicated these results with human MuSCs. We first generated a human artificial niche, similarly to the murine one. Then, we genetically modified human MuSCs by introducing the same protein that emits bioluminescence. Also in this case, only when maintained in the artificial niche, human MuSCs retained potency. Indeed, we could observe them growing following transplantation into muscles of recipient mice. Our results suggest that to maintain the potency of stem cells isolated from their native tissue, it is important to mimic the biochemical and biophysical conditions, so that the cells do not change in behavior while they are corrected. These corrected stem cells can then be transplanted, so they can regenerate the original structure and function of the tissue from where they belong. Moreover, our studies show that even a small number of MuSCs can be employed when maintained in their state of highest potential, such as quiescence as in the case of MuSCs. Artificial niches can support stem cells-based therapies to treat disorders affecting muscle tissue, or, similarly, other tissues.

Scientific Abstract:
A promising therapeutic strategy for diverse genetic disorders involves transplantation of autologous stem cells that have been genetically corrected ex vivo. A major challenge in such approaches is a loss of stem cell potency during culture. Here we describe an artificial niche for maintaining muscle stem cells (MuSCs) in vitro in a potent, quiescent state. Using a machine learning method, we identified a molecular signature of quiescence and used it to screen for factors that could maintain mouse MuSC quiescence, thus defining a quiescence medium (QM). We also engineered muscle fibers that mimic the native myofiber of the MuSC niche. Mouse MuSCs maintained in QM on engineered fibers showed enhanced potential for engraftment, tissue regeneration and self-renewal after transplantation in mice. An artificial niche adapted to human cells similarly extended the quiescence of human MuSCs in vitro and enhanced their potency in vivo. Our approach for maintaining quiescence may be applicable to stem cells isolated from other tissues.

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